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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/733,046	12/10/2003	Scott M. Walsh	BSYNEXUS-10148	8450

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EXAMINER	
FORD, VANESSA L	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 09/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/733,046	WALSH ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-46 and 55-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-46 and 55-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/19/04, 8/23/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of Group III, claims 33-46 filed on June 29, 2006 is acknowledged. Claims 1-32 and 47-54 have been cancelled. Claims 55-75 have been added. Claims 33-46 and 55-75 are pending and under examination.

Specification

2. The use of the trademark has been noted in this application. See for example, page 35. It should be capitalized wherever it appears, followed by a trademark symbol and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. Applicant is asked to review the specification for these informalities and correction is required.

Claim Objections

3. Claim 37 should recite the proper name for EDTA at the first occurrence in the claims. Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 33-46 and 55-75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for wild-type lysostaphin and wild-type nisin, does not reasonably provide enablement for lysostaphin mutants, lysostaphin variants, lysostaphin fragments or nisin variants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification enables the use of wild-type lysostaphin and nisin in a method of decolonizing bacterial populations.

The specification discloses that lysostaphin is a potent antimicrobial agent first identified in *Staphylococcus simulans* (page 3).The specification discloses that lysostaphin is a single chain polypeptide chain and has the molecular weight of approximately 27kDa (page 3). The specification discloses that nisin is a lantibiotic that a 32 amino acid, 3.4 kDa cationic peptide with five lanthionine rings produced by certain strains of *Lactococcus lactis* (page 4). The instant specification discloses that the invention encompasses lysostaphin variants (page 14). The specification discloses that lysostaphin variants can be generated by post-translational protein processing or by structural gene mutation (page 14). The instant specification teaches that nisin variants

can be generated by replacing lysines in the wild-type nisin with less polar residues (page 14).

There is no guidance provided as to which amino acids can be inserted, substituted or deleted and the polypeptide retain its biological function as a lantibiotic (e.g. lysostaphin or a nisin). The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the polypeptide determines its structural and functional properties (as a lysostaphin or nisin), predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar activity/utility requires a knowledge with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the polypeptide's structure relates to function. However, the problem of the prediction of polypeptide structure from mere sequence data of a single polypeptide and in turn utilizing predicted structural determinations to ascertain functional aspects of the polypeptide and finally what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation. There is no guidance as to what amino acids may not be changed without causing a detrimental effect to the polypeptide being claimed. The claims broadly teach polypeptides which include substitutions, insertions and/or deletions, therefore any polypeptide is being claimed, and no specific location for the deletion,

substitution or any combination thereof is recited. Thus, resulting in a polypeptide that does not function as lysostaphins or nisins or result in polypeptides that are not taught nor enabled by the specification.

Thomas E. Creighton, in his book, *"Proteins: Structures and Molecular Properties, 1984", (pages 314-315)* teaches that variation of the primary structure of a protein can result in an instable molecule. He teaches that a single amino acid change can cause a mutant hemoglobin to have lower stabilities due to any of several causes: 1) alteration of close-packing of the interior; loss of one group that normally participates in a hydrogen bond or salt bridge; 2) the introduction of a charged or polar group into the interior or the insertion into a helical region of a proline residue, which must distort the alpha-helix; 3) while sometimes radical changes of surface groups, even introduction of a non-polar side chain- have no great effect on stability.

Thomas E. Creighton, in his book "*Protein Structure: A Practical Approach, 1989; pages 184-186"* teaches that present day site directed mutagenesis of a gene allows any amino acids in a protein sequence to be changed to any other, as well as introducing deletions and insertions". The reference goes on to teach that it is difficult to know which amino acid to change and which is the best residue to substitute for the desired functional and structural effect.

Nosoh, Y. et al in *"Protein Stability and Stabilization through Protein Engineering, 1991" (chapter 7, page 197, second paragraph)* adds support to Thomas E. Creighton, by teaching that results so far accumulated on the stability and stabilization of proteins

appear to indicate that the strategy for stabilizing proteins differ from protein to protein and that any generalized mechanisms for protein stability have not yet been presented.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Therefore the specification fails to provide guidance regarding making and using peptides that are mutants, variants or fragments of lysostaphin or nisin. One of skill in the art would require guidance, in order to make or use mutants, variants or fragments of lysostaphin or nisin in a manner reasonable in correlation with the scope of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting mutants, variants or fragments having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make or use polypeptides that are in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 34 is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 34 recites "lysostaphin mutant, variant or fragment". It is unclear as to what Applicant intends, with regard to mutant, variant or fragment. Clarification is required.

6. Claim 38 is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 38 recites "nisin variant". It is unclear as to what Applicant intends? Clarification is required.

7. Claim 44 is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 44 recites "partial fatty acid". It is unclear as to what Applicant intends? Clarification is required.

8. Claim 63 is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 63 recites "partial fatty acid". It is unclear as to what Applicant intends? Clarification is required.

9. Claim 45 is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 45 contains trademarks, (e.g. SOFTISAN 378, SOFTISAN 767, SEIGEL 305, SIMUGEL 600, IMWITOR 308 and IMWITOR 742). The components in these vaccine compositions or concentrations of the vaccine components may vary, therefore the use of trademarks to a particular vaccine composition should be deleted from the claims. Correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 33-37, 39-40, 42-44, 46, 56-61 and 63-75 are rejected under 35 U.S.C. 102(b) as anticipated by Blackburn et al *(U.S. Patent 5,762,948 published June 9, 1998).*

The claims are drawn to a method of decolonizing populations comprising topically applying to a patient in need thereof at a bacterially infected site a topical composition comprising lysostaphin and one or more lantibiotics.

Blackburn et al teach a method of disinfecting (decolonizing) bacterial populations comprising topically applying to a patient a topical composition comprising nisin and one or more lantibiotics such as lysostaphin (the Abstract, column 3 and columns 11 –12, Example 7). Blackburn et al teach that the lantibiotics are present at 25

ug/ml in the compositions (column 8, Table I). Therefore the prior art teaches a topical composition comprising a antibiotic from about 0.1 to about 10.0 wt %. Blackburn et al teach the compositions of the invention comprise chelating agents such as EDTA (column 3), a carrier for topical application such as a wipe or liquid (see the Abstract, column 3 and column 5), anti-infective active agents such as such as chlorhexidine (column 3), a skin absorption promoter such as monoglycerides and fatty acids (column 4) and surfactants such as polysorbate 20 (column 4). Blackburn et al teach that composition can comprise emulsifers (column 4). Blackburn et al teach a reduction in Staphylococcus aureus (columns 12-14). Claim limitations such as "wherein the concentration of lysostaphin in said composition is lower than the minimum inhibitory concentration of lysostaphin when used independently", "wherein the concentration of lantibiotic in said composition is lower than the minimum inhibitory concentration of lantibiotic when used independently", wherein the concentration of lysostaphin and lantibiotic in said composition is lower than the minimum inhibitory concentration of lysostaphin and lantibiotic when used independently" would be inherent in the teaching of the prior art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 33-37, 39-40, 42-44, 46 and 55-75 are rejected under 35 U.S.C. 103(a) as unpatentable over Daley et al *(U.S. Patent No. 5, 342, 612 published August 1994)* in view of Blackburn et al *(U.S. Patent No. 4,980, 163 published December 25, 1990).*

The claims are drawn to a method of decolonizing populations comprising topically applying to a patient in need thereof at a bacterially infected site a topical composition comprising lysostaphin and one or more lantibiotics.

Daley et al teach a method of eliminating bacterial (*Staphlyococcus)* infections in bovine mammary glands comprising administering a composition comprising bacteriostatic peptide such as lysostaphin or nisin (column 4 and columns 11-13). Daley et al teach that the compositions of the invention contain 0.01% to about 50% by weight of the bacteriostatic peptide in the total composition (column 4). Daley et al do not teach using other lantibiotics in the method of the invention.

Blackburn et al teach compositions comprising bactericides (see the Abstract). Blackburn et al teach compositions comprising lysostaphin, nisin a chelating agent such as EDTA and a surfactant (the Abstract and columns 3-4). Blackburn et al teach that compositions may include antibiotics, copolymers and surfactants which include emulsifers and fatty acids (column 4). Blackburn et al teach that suitable carrier for the bactericides include organic solvents, buffers and polymers (column 4). Blackburn et al teach that compositions of the invention have enhanced broad range bactericide activity against bacteria such as *S. aureus* and *P. aeruginosa* (claims 18 and 19). Blackburn et al teach that the concentration of lysostaphin is about 0.1 to 100 μg/ml and the concentration of nisin is between about 0.1 and 300 100 μg/ml (column 4 and claims 20-

21). Blackburn et al teach the compositions comprising lysostaphin and nisin provide broad range bactericidal activity against bacterial infections (see the Abstract and columns 6-7). Blackburn et al the teach that bactericidal activity and the overall speed of bactericidal activity is enhanced when two bacteriocins are combined in one composition (column 2). Claim limitations regarding how many time the composition is applied to the infected site would be a matter of optimizing experimental parameters (see claims 68-71).

It would be *prima facie* obvious at the time the invention was made to modify he method of eliminating bacterial infections as taught by Daley et al to administer to a patient with a bacterial infection (*S. aureus* and *P. aeruginosa* infections) because Blackburn et al discloses that a composition comprising lysostaphin and nisin provide broad range bactericidal activity against bacterial infections and the overall speed of bactericidal activity is enhanced when two bacteriocins are combined in one composition.

Status of Claims

12. No claims are allowed.

Conclusion

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vanessa L. Ford whose telephone number is (571) 272-0857. The examiner can normally be reached on 9 am- 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Albert Navarro can be reached on (571) 272-0861. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Vanessa L. Ford
Biotechnology Patent Examiner
August 28, 2006

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PRIMARY EXAMINER